ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets
Ferriprox 1 000 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ferriprox 500 mg film-coated tablets

Each tablet contains 500 mg deferiprone.

Ferriprox 1 000 mg film-coated tablets

Each tablet contains 1 000 mg deferiprone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Ferriprox 500 mg film-coated tablets

White to off-white, capsule-shaped, film-coated tablet imprinted “APO” bisect “500” on one side, plain on the other. The tablet is 7.1 mm x 17.5 mm x 6.8 mm and scored. The tablet can be divided into equal halves.

Ferriprox 1 000 mg film-coated tablets

White to off-white, capsule-shaped, film-coated tablet imprinted “APO” bisect “1000” on one side, plain on the other. The tablet is 7.9 mm x 19.1 mm x 7 mm and scored. The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

Ferriprox in combination with another chelator (see section 4.4) is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see section 4.2).

4.2 Posology and method of administration

Deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassaemia.

Posology

Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest half tablet. See tables below for recommended doses for body weights at 10 kg increments.

To obtain a dose of about 75 mg/kg/day, use the number of tablets suggested in the following tables for the body weight of the patient. Sample body weights at 10 kg increments are listed.

Table 1a: Dose table for Ferriprox 500 mg film-coated tablets

Body weight (kg)	**Total daily dose (mg)**	**Dose (mg, three times/day)**	**Number of tablets (three times/day)**
20	1 500	500	1.0
30	2 250	750	1.5
40	3 000	1 000	2.0
50	3 750	1 250	2.5
60	4 500	1 500	3.0
70	5 250	1 750	3.5
80	6 000	2 000	4.0
90	6 750	2 250	4.5

Table 1b: Dose table for Ferriprox 1 000 mg film-coated tablets

Body weight (kg)	**Total daily dose (mg)**	**Number of 1 000 mg tablets***		
		Morning	**Midday**	**Evening**
20	1 500	0.5	0.5	0.5
30	2 250	1.0	0.5	1.0
40	3 000	1.0	1.0	1.0
50	3 750	1.5	1.0	1.5
60	4 500	1.5	1.5	1.5
70	5 250	2.0	1.5	2.0
80	6 000	2.0	2.0	2.0
90	6 750	2.5	2.0	2.5

*number of tablets rounded to nearest half tablet

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Dose adjustment
The effect of Ferriprox in decreasing the body iron is directly influenced by the dose and the degree of iron overload. After starting Ferriprox therapy, it is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l.

Dose adjustments when used with other iron chelators
In patients for whom monotherapy is inadequate, Ferriprox may be used with deferoxamine at the standard dose (75 mg/kg/day) but should not exceed 100 mg/kg/day.

In the case of iron-induced heart failure, Ferriprox at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted.

Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal.

Renal impairment
Dose adjustment is not required in patients with mild, moderate, or severe renal impairment (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease are unknown.

Hepatic impairment
Dose adjustment is not required in patients with mildly or moderately impaired hepatic function (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment are unknown.

Paediatric population
There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breast-feeding (see section 4.6).
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia/Agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis (see section 4.8 'Description of selected adverse reactions'). The patient's absolute neutrophil count (ANC) should be monitored every week during the first year of therapy. For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of deferiprone therapy.

The change from weekly ANC monitoring to monitoring at the time of transfusion visits after 12 months of Ferriprox therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy (see section 4.4 below).

In clinical studies, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on deferiprone, therapy should be immediately interrupted, and an ANC obtained without delay. The neutrophil count should be then monitored more frequently.

Patients should be aware to contact their physician if they experience any symptoms indicative of infection (such as fever, sore throat and flu-like symptoms). Immediately interrupt deferiprone if the patient experiences infection.

Suggested management of cases of neutropenia is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on deferiprone treatment.

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher if the baseline ANC is less than $1.5x10^9$/l.

For neutropenia events (ANC < $1.5x10^9$/l and > $0.5x10^9$/l):

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient has fully recovered. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed, and an appropriate therapeutic regimen instituted.

For agranulocytosis (ANC < $0.5x10^9$/l):

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, rechallenge is contraindicated.

Carcinogenicity/mutagenicity

In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3).

Plasma zinc (Zn^{2+}) concentration

Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

Human immunodeficiency virus (HIV) positive or other immunocompromised patients

No data are available on the use of deferiprone in HIV positive or in other immunocompromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immunocompromised patients should not be initiated unless potential benefits outweigh potential risks.

Renal or hepatic impairment and liver fibrosis

There are no data available on the use of deferiprone in patients with end stage renal disease or severe hepatic impairment (see section 5.2). Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be monitored in these patient populations during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Discolouration of urine

Patients should be informed that their urine may show a reddish/brown discolouration due to the excretion of the iron-deferiprone complex.

Neurological disorders

Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but have also been observed with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

Combined use with other iron chelators

The use of combination therapy should be considered on a case-by-case basis. The response to therapy should be assessed periodically, and the occurrence of adverse events closely monitored. Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine. Combination therapy with deferoxamine is not recommended when monotherapy with either chelator is adequate or when serum ferritin falls below 500 µg/l. Limited data are available on the combined use of Ferriprox and deferasirox, and caution should be applied when considering the use of such combination.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.3).

Since deferiprone binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids and deferiprone.

The safety of concurrent use of deferiprone and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between deferoxamine and vitamin C, caution should be used when administering deferiprone and vitamin C concurrently.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in men and women

Due to the genotoxic potential of deferiprone (see section 5.3), women of childbearing potential are recommended to use effective contraceptive measures and avoid becoming pregnant while being treated with Ferriprox and for 6 months following the completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and for 3 months following completion of treatment.

Pregnancy

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pregnant women must be advised to immediately stop taking deferiprone (see section 4.3).

Breast-feeding

It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breast-feeding mothers. If treatment is unavoidable, breast-feeding must be stopped (see section 4.3).

Fertility

No effects on fertility or early embryonic development were noted in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during therapy with deferiprone in clinical studies were nausea, vomiting, abdominal pain, and chromaturia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical studies with deferiprone was agranulocytosis, defined as an absolute neutrophil count less than $0.5x10^9$/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

Tabulated list of adverse reactions

Adverse reaction frequencies: very common (≥ 1/10), common (≥ 1/100 to < 1/10), not known (cannot be estimated from the available data).

Table 2: List of adverse reactions

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Frequency not known**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal pain Vomiting	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Description of selected adverse reactions

The most serious adverse reaction reported in clinical studies with deferiprone is agranulocytosis (neutrophils < $0.5x10^9$/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). Data from pooled clinical studies in patients with systemic iron overload showed that 63% of the episodes of agranulocytosis occurred within the first six months of treatment, 74% within the first year and 26% after one year of therapy. The median time to onset of the first episode of agranulocytosis was 190 days (ranged 22 days- 17.6 years) and median duration was 10 days in clinical studies. A fatal outcome was observed in 8.3% of the reported episodes of agranulocytosis from clinical studies and post-marketing experience.

The observed incidence of the less severe form of neutropenia (neutrophils < $1.5x10^9$/l) is 4.9% (2.5 cases per 100 patient-years). This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Episodes of diarrhoea, mostly mild and transient, have been reported in patients treated with deferiprone. Gastrointestinal effects are more frequent at the beginning of therapy and resolve in most patients within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

Increased levels of serum liver enzymes have been reported in some patients taking deferiprone. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone (see section 4.4).

Some patients experienced progression of fibrosis associated with an increase in iron overload or hepatitis C.

Low plasma zinc levels have been associated with deferiprone in a minority of patients. The levels normalised with oral zinc supplementation.

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

The safety profile of combination therapy (deferiprone and deferoxamine) observed in clinical studies, post-marketing experience or published literature was consistent with that characterised for monotherapy.

Data from the pooled safety database from clinical studies (1 343 patient-years exposure to Ferriprox monotherapy and 244 patient-years exposure to Ferriprox and deferoxamine) showed statistically significant ($p < 0.05$) differences in the incidence of adverse reactions based on System Organ Class for “Cardiac disorders", "Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders". The incidences of “Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of “Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of “Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy. Careful monitoring of cardiac events in patients on combination therapy is warranted (see section 4.4).

The incidences of adverse reactions experienced by 18 children and 97 adults treated with combination therapy were not significantly different between the two age groups except in the incidence of arthropathy (11.1% in children vs. none in adults, p=0.02). Evaluation of rate of reactions per 100 patient-years of exposure showed that only the rate of diarrhoea was significantly higher in children (11.1) than in adults (2.0, p=0.01).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of acute overdose have been reported. However, neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation.

In case of overdose, close clinical supervision of the patient is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, iron chelating agents, ATC code: V03AC02

Mechanism of action

The active substance is deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a bidentate ligand which binds iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a total dose of 75 mg/kg per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. Data from the published literature on iron balance studies in patients with thalassaemia major show that the use of Ferriprox concurrently with deferoxamine (coadministration of both chelators during the same day, either simultaneously or sequentially, e.g., Ferriprox during the day and deferoxamine during the night), promotes greater iron excretion than either medicinal product alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety

Clinical efficacy studies were conducted with 500 mg film-coated tablets.

Studies LA16-0102, LA-01 and LA08-9701 compared the efficacy of Ferriprox with that of deferoxamine in controlling serum ferritin in transfusion-dependent thalassaemia patients. Ferriprox and deferoxamine were equivalent in promoting a net stabilisation or reduction of body iron load, despite the continuous transfusional iron administration in those patients (no difference in proportion

of patients with a negative trend in serum ferritin between the two treatment groups by regression analysis; $p > 0.05$).

A magnetic resonance imaging (MRI) method, T2*, was also used to quantify myocardial iron load. Iron overload causes concentration-dependent MRI T2* signal loss, thus, increased myocardial iron reduces myocardial MRI T2* values. Myocardial MRI T2* values of less than 20 ms represent iron overload in the heart. An increase in MRI T2* on treatment indicates that iron is being removed from the heart. A positive correlation between MRI T2* values and cardiac function (as measured by left ventricular ejection fraction (LVEF)) has been documented.

Study LA16-0102 compared the efficacy of Ferriprox with that of deferoxamine in decreasing cardiac iron overload and in improving cardiac function (as measured by LVEF) in transfusion-dependent thalassaemia patients. Sixty-one patients with cardiac iron overload, previously treated with deferoxamine, were randomised to continue deferoxamine (average dose 43 mg/kg/day; N=31) or to switch to Ferriprox (average dose 92 mg/kg/day N=29). Over the 12-month duration of the study, Ferriprox was superior to deferoxamine in decreasing cardiac iron load. There was an improvement in cardiac T2* of more than 3 ms in patients treated with Ferriprox compared with a change of about 1 ms in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (difference between groups; $p=0.003$).

Study LA12-9907 compared survival, incidence of cardiac disease, and progression of cardiac disease in 129 patients with thalassaemia major treated for at least 4 years with Ferriprox (N=54) or deferoxamine (N=75). Cardiac endpoints were assessed by echocardiogram, electrocardiogram, the New York Heart Association classification and death due to cardiac disease. There was no significant difference in the percentage of patients with cardiac dysfunction at first assessment (13% for Ferriprox vs. 16% for deferoxamine). Of patients with cardiac dysfunction at first assessment, none treated with deferiprone compared with four (33%) treated with deferoxamine had worsening of their cardiac status ($p=0.245$). Newly diagnosed cardiac dysfunction occurred in 13 (20.6%) deferoxamine-treated patients and in 2 (4.3%) Ferriprox-treated patients who were cardiac disease-free at the first assessment ($p=0.013$). Overall, fewer Ferriprox-treated patients than deferoxamine-treated patients showed a worsening of cardiac dysfunction from first to last assessment (4% vs. 20%, $p=0.007$).

Data from the published literature are consistent with the results from the company-sponsored studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.

A randomized, placebo-controlled, double-blind study evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (34.9 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (43.4 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1 574 µg/l to 598 µg/l with concurrent therapy vs. 1 379 µg/l to 1 146 µg/l with deferoxamine monotherapy, $p < 0.001$), significantly greater reduction in myocardial iron overload, as assessed by an increase in MRI T2* (11.7 ms to 17.7 ms with concurrent therapy vs. 12.4 ms to 15.7 ms with deferoxamine monotherapy, $p=0.02$) and significantly greater reduction in liver iron concentration, also assessed by an increase in MRI T2* (4.9 ms to 10.7 ms with concurrent therapy vs. 4.2 ms to 5.0 ms with deferoxamine monotherapy, $p < 0.001$).

Study LA37-1111 was conducted to evaluate the effect of single therapeutic (33 mg/kg) and supratherapeutic (50 mg/kg) oral doses of deferiprone on the cardiac QT interval duration in healthy subjects. The maximum difference between the LS means of the therapeutic dose and placebo was 3.01 ms (95% one-sided UCL: 5.01 ms), and between the LS means of the supratherapeutic dose and placebo was 5.23 ms (95% one-sided UCL: 7.19 ms). Ferriprox was concluded to produce no significant prolongation of the QT interval.

5.2 Pharmacokinetic properties

Absorption

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration occurs 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85 µmol/l) than in the fasting state (126 µmol/l), although there was no decrease in the amount of deferiprone absorbed when it was given with food.

Biotransformation

Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capability due to inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of deferiprone.

Elimination

In humans, deferiprone is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. A variable amount of elimination via the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

Renal impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR $\geq$ 90 mL/min/1.73m^2), mild renal impairment (eGFR 60-89 mL/min/1.73m^2), moderate renal impairment (eGFR 30-59 mL/min/1.73m^2), and severe renal impairment (eGFR 15–29 mL/min/1.73m^2). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC.

Regardless of the degree of renal impairment, the majority of the dose of Ferriprox was excreted in the urine over the first 24 hours as deferiprone 3-*O*-glucuronide. No significant effect of renal impairment was seen on systemic exposure to deferiprone. Systemic exposure to the inactive 3-*O*-glucuronide increased with decreasing eGFR. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with impaired renal function. The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease is unknown.

Hepatic impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC. Deferiprone AUCs did not differ between treatment groups, but C_{max} was decreased by 20% in mildly or moderately hepatically impaired subjects compared with healthy volunteers. Deferiprone-3-*O*-glucuronide AUC was decreased by 10% and C_{max} by 20% in mildly and moderately impaired subjects compared with healthy volunteers. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with mildly or moderately impaired hepatic function.

The influence of severe hepatic impairment on the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide has not been evaluated. The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Non-clinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased white blood cell (WBC), red blood cell (RBC) and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties; however, it did display clastogenic characteristics in *in vitro* assays and in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded pregnant rats and rabbits at doses at least as low as 25 mg/kg/day. No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally at doses of up to 75 mg/kg twice daily for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the oestrous cycle delayed time to confirmed mating at all doses tested.

No prenatal and postnatal reproductive studies have been conducted in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ferriprox 500 mg film-coated tablets

Tablet core
Microcrystalline cellulose
Magnesium stearate
Colloidal anhydrous silica

Coating
Hypromellose
Macrogol 3350
Titanium dioxide

Ferriprox 1 000 mg film-coated tablets

Tablet core
Methylcellulose 12 to 18 mPas
Crospovidone
Magnesium stearate

Coating
Hypromellose 2910
Hydroxypropyl cellulose
Macrogol 8000
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Ferriprox 500 mg film-coated tablets

5 years.

Ferriprox 1 000 mg film-coated tablets

4 years.
After first opening, use within 50 days.

6.4 Special precautions for storage

Ferriprox 500 mg film-coated tablets

Do not store above 30 ºC.

Ferriprox 1 000 mg film-coated tablets

Do not store above 30 ºC.
Keep the bottle tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Ferriprox 500 mg film-coated tablets

High density polyethylene (HDPE) bottle with a child resistant polypropylene cap.
Pack size of 100 tablets.

Ferriprox 1 000 mg film-coated tablets

High density polyethylene (HDPE) bottle with a child resistant polypropylene cap and a desiccant.
Pack size of 50 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER

Ferriprox 500 mg film-coated tablets

EU/1/99/108/001

Ferriprox 1 000 mg film-coated tablets

EU/1/99/108/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 1999
Date of latest renewal: 21 September 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral solution contains 100 mg deferiprone (25 g deferiprone in 250 ml and 50 g deferiprone in 500 ml).

Excipient with known effect

Each ml of oral solution contains 0.4 mg sunset yellow (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution.

Clear, reddish orange-coloured liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ferriprox monotherapy is indicated for the treatment of iron overload in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

Ferriprox in combination with another chelator (see section 4.4) is indicated in patients with thalassaemia major when monotherapy with any iron chelator is ineffective, or when prevention or treatment of life-threatening consequences of iron overload (mainly cardiac overload) justifies rapid or intensive correction (see section 4.2).

4.2 Posology and method of administration

Deferiprone therapy should be initiated and maintained by a physician experienced in the treatment of patients with thalassaemia.

Posology

Deferiprone is usually given as 25 mg/kg body weight, orally, three times a day for a total daily dose of 75 mg/kg body weight. Dose per kilogram body weight should be calculated to the nearest 2.5 ml. See table below for recommended doses for body weights at 10 kg increments.

To obtain a dose of about 75 mg/kg/day, use the volume of oral solution suggested in the following table for the body weight of the patient. Sample body weights at 10 kg increments are listed.

Table 1: Dose table for Ferriprox 100 mg/ml oral solution

Body weight (kg)	**Total daily dose (mg)**	**Dose (mg, three times/day)**	**ml of oral solution (three times/day)**
20	1 500	500	5.0
30	2 250	750	7.5
40	3 000	1 000	10.0
50	3 750	1 250	12.5
60	4 500	1 500	15.0
70	5 250	1 750	17.5
80	6 000	2 000	20.0
90	6 750	2 250	22.5

A total daily dose above 100 mg/kg body weight is not recommended because of the potentially increased risk of adverse reactions (see sections 4.4, 4.8, and 4.9).

Dose adjustment
The effect of Ferriprox in decreasing the body iron is directly influenced by the dose and the degree of iron overload. After starting Ferriprox therapy, it is recommended that serum ferritin concentrations, or other indicators of body iron load, be monitored every two to three months to assess the long-term effectiveness of the chelation regimen in controlling the body iron load. Dose adjustments should be tailored to the individual patient's response and therapeutic goals (maintenance or reduction of body iron burden). Interruption of therapy with deferiprone should be considered if serum ferritin falls below 500 µg/l.

Dose adjustments when used with other iron chelators
In patients for whom monotherapy is inadequate, Ferriprox may be used with deferoxamine at the standard dose (75 mg/kg/day) but should not exceed 100 mg/kg/day.

In the case of iron-induced heart failure, Ferriprox at 75-100 mg/kg/day should be added to deferoxamine therapy. The product information of deferoxamine should be consulted.

Concurrent use of iron chelators is not recommended in patients whose serum ferritin falls below 500 µg/l due to the risk of excessive iron removal.

Renal impairment
Dose adjustment is not required in patients with mild, moderate, or severe renal impairment (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease are unknown.

Hepatic impairment
Dose adjustment is not required in patients with mildly or moderately impaired hepatic function (see section 5.2). The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment are unknown.

Paediatric population
There are limited data available on the use of deferiprone in children between 6 and 10 years of age, and no data on deferiprone use in children under 6 years of age.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- History of recurrent episodes of neutropenia.
- History of agranulocytosis.
- Pregnancy (see section 4.6).
- Breast-feeding (see section 4.6).
- Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia/Agranulocytosis

Deferiprone has been shown to cause neutropenia, including agranulocytosis (see section 4.8 'Description of selected adverse reactions'). The patient's absolute neutrophil count (ANC) should be monitored every week during the first year of therapy. For patients whose Ferriprox has not been interrupted during the first year of therapy due to any decrease in the neutrophil count, the frequency of ANC monitoring may be extended to the patient's blood transfusion interval (every 2-4 weeks) after one year of deferiprone therapy.

The change from weekly ANC monitoring to monitoring at the time of transfusion visits after 12 months of Ferriprox therapy, should be considered on an individual patient basis, according to the physician's assessment of the patient's understanding of the risk minimization measures required during therapy (see section 4.4 below).

In clinical studies, weekly monitoring of the neutrophil count has been effective in identifying cases of neutropenia and agranulocytosis. Agranulocytosis and neutropenia usually resolve upon discontinuation of Ferriprox, but fatal cases of agranulocytosis have been reported. If the patient develops an infection while on deferiprone, therapy should be immediately interrupted, and an ANC obtained without delay. The neutrophil count should be then monitored more frequently.

Patients should be aware to contact their physician if they experience any symptoms indicative of infection (such as fever, sore throat and flu-like symptoms). Immediately interrupt deferiprone if the patient experiences infection.

Suggested management of cases of neutropenia is outlined below. It is recommended that such a management protocol be in place prior to initiating any patient on deferiprone treatment.

Treatment with deferiprone should not be initiated if the patient is neutropenic. The risk of agranulocytosis and neutropenia is higher if the baseline ANC is less than $1.5x10^9$/l.

For neutropenia events (ANC < $1.5x10^9$/l and > $0.5x10^9$/l):

Instruct the patient to immediately discontinue deferiprone and all other medicinal products with a potential to cause neutropenia. The patient should be advised to limit contact with other individuals in order to reduce the risk of infection. Obtain a complete blood cell (CBC) count, with a white blood cell (WBC) count, corrected for the presence of nucleated red blood cells, a neutrophil count, and a platelet count immediately upon diagnosing the event and then repeat daily. It is recommended that following recovery from neutropenia, weekly CBC, WBC, neutrophil and platelet counts continue to be obtained for three consecutive weeks, to ensure that the patient has fully recovered. Should any evidence of infection develop concurrently with the neutropenia, the appropriate cultures and diagnostic procedures should be performed, and an appropriate therapeutic regimen instituted.

For agranulocytosis (ANC < $0.5x10^9$/l):

Follow the guidelines above and administer appropriate therapy such as granulocyte colony stimulating factor, beginning the same day that the event is identified; administer daily until the condition resolves. Provide protective isolation and if clinically indicated, admit patient to the hospital.

Limited information is available regarding rechallenge. Therefore, in the event of neutropenia, rechallenge is not recommended. In the event of agranulocytosis, rechallenge is contraindicated.

Carcinogenicity/mutagenicity

In view of the genotoxicity results, a carcinogenic potential of deferiprone cannot be excluded (see section 5.3).

Plasma zinc (Zn^{2+}) concentration

Monitoring of plasma Zn^{2+} concentration, and supplementation in case of a deficiency, is recommended.

Human immunodeficiency virus (HIV) positive or other immunocompromised patients

No data are available on the use of deferiprone in HIV positive or in other immunocompromised patients. Given that deferiprone can be associated with neutropenia and agranulocytosis, therapy in immunocompromised patients should not be initiated unless potential benefits outweigh potential risks.

Renal or hepatic impairment and liver fibrosis

There are no data available on the use of deferiprone in patients with end stage renal disease or severe hepatic impairment (see section 5.2). Caution must be exercised in patients with end stage renal disease or severe hepatic dysfunction. Renal and hepatic function should be monitored in these patient populations during deferiprone therapy. If there is a persistent increase in serum alanine aminotransferase (ALT), interruption of deferiprone therapy should be considered.

In thalassaemia patients there is an association between liver fibrosis and iron overload and/or hepatitis C. Special care must be taken to ensure that iron chelation in patients with hepatitis C is optimal. In these patients careful monitoring of liver histology is recommended.

Discolouration of urine

Patients should be informed that their urine may show a reddish/brown discolouration due to the excretion of the iron-deferiprone complex.

Neurological disorders

Neurological disorders have been observed in children treated with more than 2.5 times the maximum recommended dose for several years but have also been observed with standard doses of deferiprone. Prescribers are reminded that the use of doses above 100 mg/kg/day are not recommended. Deferiprone use should be discontinued if neurological disorders are observed (see sections 4.8 and 4.9).

Combined use with other iron chelators

The use of combination therapy should be considered on a case-by-case basis. The response to therapy should be assessed periodically, and the occurrence of adverse events closely monitored. Fatalities and life-threatening situations (caused by agranulocytosis) have been reported with deferiprone in combination with deferoxamine. Combination therapy with deferoxamine is not recommended when

monotherapy with either chelator is adequate or when serum ferritin falls below 500 µg/l. Limited data are available on the combined use of Ferriprox and deferasirox, and caution should be applied when considering the use of such combination.

Excipients

Ferriprox oral solution contains the colouring agent sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the unknown mechanism of deferiprone-induced neutropenia, patients must not take medicinal products known to be associated with neutropenia or those that can cause agranulocytosis (see section 4.3).

Since deferiprone binds to metallic cations, the potential exists for interactions between deferiprone and trivalent cation-dependent medicinal products such as aluminium-based antacids. Therefore, it is not recommended to concomitantly ingest aluminium-based antacids and deferiprone.

The safety of concurrent use of deferiprone and vitamin C has not been formally studied. Based on the reported adverse interaction that can occur between deferoxamine and vitamin C, caution should be used when administering deferiprone and vitamin C concurrently.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in men and women

Due to the genotoxic potential of deferiprone (see section 5.3), women of childbearing potential are recommended use effective contraceptive measures and avoid becoming pregnant while being treated with Ferriprox and for 6 months following the completion of treatment. .

Men are recommended to use effective contraceptive measures and to not father a child while receiving Ferriprox and for 3 months following completion of treatment.

Pregnancy

There are no adequate data from the use of deferiprone in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pregnant women must be advised to immediately stop taking deferiprone (see section 4.3).

Breast-feeding

It is not known whether deferiprone is excreted in human milk. No prenatal and postnatal reproductive studies have been conducted in animals. Deferiprone must not be used by breast-feeding mothers. If treatment is unavoidable, breast-feeding must be stopped (see section 4.3).

Fertility

No effects on fertility or early embryonic development were noted in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported during therapy with deferiprone in clinical studies were nausea, vomiting, abdominal pain, and chromaturia, which were reported in more than 10% of patients. The most serious adverse reaction reported in clinical studies with deferiprone was agranulocytosis, defined as an absolute neutrophil count less than $0.5x10^9$/l, which occurred in approximately 1% of patients. Less severe episodes of neutropenia were reported in approximately 5% of patients.

Tabulated list of adverse reactions

Adverse reaction frequencies: very common (≥ 1/10), common (≥ 1/100 to < 1/10), not known (cannot be estimated from the available data).

Table 2: List of adverse reactions

System organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Frequency not known**
Blood and lymphatic system disorders		Neutropenia Agranulocytosis	
Immune system disorders			Hypersensitivity reactions
Metabolism and nutrition disorders		Increased appetite	
Nervous system disorders		Headache	
Gastrointestinal disorders	Nausea Abdominal pain Vomiting	Diarrhoea	
Skin and subcutaneous tissue disorders			Rash Urticaria
Musculoskeletal and connective tissue disorders		Arthralgia	
Renal and urinary disorders	Chromaturia		
General disorders and administration site conditions		Fatigue	
Investigations		Increased liver enzymes	

Description of selected adverse reactions

The most serious adverse reaction reported in clinical studies with deferiprone is agranulocytosis (neutrophils < $0.5x10^9$/l), with an incidence of 1.1% (0.6 cases per 100 patient-years of treatment) (see section 4.4). Data from pooled clinical studies in patients with systemic iron overload showed that 63% of the episodes of agranulocytosis occurred within the first six months of treatment, 74% within the first year and 26% after one year of therapy. The median time to onset of the first episode of agranulocytosis was 190 days (ranged 22 days- 17.6 years) and median duration was 10 days in clinical studies. A fatal outcome was observed in 8.3% of the reported episodes of agranulocytosis from clinical studies and post-marketing experience.

The observed incidence of the less severe form of neutropenia (neutrophils < $1.5x10^9$/l) is 4.9% (2.5 cases per 100 patient-years). This rate should be considered in the context of the underlying elevated incidence of neutropenia in thalassaemia patients, particularly in those with hypersplenism.

Episodes of diarrhoea, mostly mild and transient, have been reported in patients treated with deferiprone. Gastrointestinal effects are more frequent at the beginning of therapy and resolve in most patients within a few weeks without the discontinuation of treatment. In some patients it may be beneficial to reduce the dose of deferiprone and then scale it back up to the former dose. Arthropathy events, which ranged from mild pain in one or more joints to severe arthritis with effusion and significant disability, have also been reported in patients treated with deferiprone. Mild arthropathies are generally transient.

Increased levels of serum liver enzymes have been reported in some patients taking deferiprone. In the majority of these patients, the increase was asymptomatic and transient, and returned to baseline without discontinuation or decreasing the dose of deferiprone (see section 4.4).

Some patients experienced progression of fibrosis associated with an increase in iron overload or hepatitis C.

Low plasma zinc levels have been associated with deferiprone in a minority of patients. The levels normalised with oral zinc supplementation.

Neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. Episodes of hypotonia, instability, inability to walk, and hypertonia with inability of limb movement, have been reported in children in the post-marketing setting with standard doses of deferiprone. The neurological disorders progressively regressed after deferiprone discontinuation (see sections 4.4 and 4.9).

The safety profile of combination therapy (deferiprone and deferoxamine) observed in clinical studies, post-marketing experience or published literature was consistent with that characterised for monotherapy.

Data from the pooled safety database from clinical studies (1 343 patient-years exposure to Ferriprox monotherapy and 244 patient-years exposure to Ferriprox and deferoxamine) showed statistically significant ($p<0.05$) differences in the incidence of adverse reactions based on System Organ Class for “Cardiac disorders", "Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders". The incidences of “Musculoskeletal and connective tissue disorders” and "Renal and urinary disorders" were lower during combination therapy than monotherapy, whereas the incidence of “Cardiac disorders" was higher during combination therapy than monotherapy. The higher rate of “Cardiac disorders" reported during combination therapy than monotherapy was possibly due to the higher incidence of pre-existing cardiac disorders in patients who received combination therapy. Careful monitoring of cardiac events in patients on combination therapy is warranted (see section 4.4).

The incidences of adverse reactions experienced by 18 children and 97 adults treated with combination therapy were not significantly different between the two age groups except in the incidence of arthropathy (11.1% in children vs. none in adults, $p=0.02$). Evaluation of rate of reactions per 100 patient-years of exposure showed that only the rate of diarrhoea was significantly higher in children (11.1) than in adults (2.0, $p=0.01$).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of acute overdose have been reported. However, neurological disorders (such as cerebellar symptoms, diplopia, lateral nystagmus, psychomotor slowdown, hand movements and axial hypotonia) have been observed in children who had been voluntarily prescribed more than 2.5 times the maximum recommended dose of 100 mg/kg/day for several years. The neurological disorders progressively regressed after deferiprone discontinuation.

In case of overdose, close clinical supervision of the patient is required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: All other therapeutic products, iron chelating agents, ATC code: V03AC02

Mechanism of action

The active substance is deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one), a bidentate ligand which binds iron in a 3:1 molar ratio.

Pharmacodynamic effects

Clinical studies have demonstrated that Ferriprox is effective in promoting iron excretion and that a total dose of 75 mg/kg per day can prevent the progression of iron accumulation as assessed by serum ferritin, in patients with transfusion-dependent thalassaemia. Data from the published literature on iron balance studies in patients with thalassaemia major show that the use of Ferriprox concurrently with deferoxamine (coadministration of both chelators during the same day, either simultaneously or sequentially, e.g., Ferriprox during the day and deferoxamine during the night), promotes greater iron excretion than either medicinal product alone. Doses of Ferriprox in those studies ranged from 50 to 100 mg/kg/day and doses of deferoxamine from 40 to 60 mg/kg/day. However, chelation therapy may not necessarily protect against iron-induced organ damage.

Clinical efficacy and safety

Clinical efficacy studies were conducted with 500 mg film-coated tablets.

Studies LA16-0102, LA-01 and LA08-9701 compared the efficacy of Ferriprox with that of deferoxamine in controlling serum ferritin in transfusion-dependent thalassaemia patients. Ferriprox and deferoxamine were equivalent in promoting a net stabilisation or reduction of body iron load, despite the continuous transfusional iron administration in those patients (no difference in proportion of patients with a negative trend in serum ferritin between the two treatment groups by regression analysis; $p > 0.05$).

A magnetic resonance imaging (MRI) method, T2*, was also used to quantify myocardial iron load. Iron overload causes concentration-dependent MRI T2* signal loss, thus, increased myocardial iron reduces myocardial MRI T2* values. Myocardial MRI T2* values of less than 20 ms represent iron overload in the heart. An increase in MRI T2* on treatment indicates that iron is being removed from the heart. A positive correlation between MRI T2* values and cardiac function (as measured by left ventricular ejection fraction (LVEF)) has been documented.

Study LA16-0102 compared the efficacy of Ferriprox with that of deferoxamine in decreasing cardiac iron overload and in improving cardiac function (as measured by LVEF) in transfusion-dependent thalassaemia patients. Sixty-one patients with cardiac iron overload, previously treated with deferoxamine, were randomised to continue deferoxamine (average dose 43 mg/kg/day; N=31) or to

switch to Ferriprox (average dose 92 mg/kg/day N=29). Over the 12-month duration of the study, Ferriprox was superior to deferoxamine in decreasing cardiac iron load. There was an improvement in cardiac T2* of more than 3 ms in patients treated with Ferriprox compared with a change of about 1 ms in patients treated with deferoxamine. At the same time point, LVEF had increased from baseline by 3.07 ± 3.58 absolute units (%) in the Ferriprox group and by 0.32 ± 3.38 absolute units (%) in the deferoxamine group (difference between groups; p=0.003).

Study LA12-9907 compared survival, incidence of cardiac disease, and progression of cardiac disease in 129 patients with thalassaemia major treated for at least 4 years with Ferriprox (N=54) or deferoxamine (N=75). Cardiac endpoints were assessed by echocardiogram, electrocardiogram, the New York Heart Association classification and death due to cardiac disease. There was no significant difference in the percentage of patients with cardiac dysfunction at first assessment (13% for Ferriprox vs. 16% for deferoxamine). Of patients with cardiac dysfunction at first assessment, none treated with deferiprone compared with four (33%) treated with deferoxamine had worsening of their cardiac status (p=0.245). Newly diagnosed cardiac dysfunction occurred in 13 (20.6%) deferoxamine-treated patients and in 2 (4.3%) Ferriprox-treated patients who were cardiac disease-free at the first assessment (p=0.013). Overall, fewer Ferriprox-treated patients than deferoxamine-treated patients showed a worsening of cardiac dysfunction from first to last assessment (4% vs. 20%, p=0.007).

Data from the published literature are consistent with the results from the company-sponsored studies, demonstrating less heart disease and/or increased survival in Ferriprox-treated patients than in those treated with deferoxamine.

A randomized, placebo-controlled, double-blind study evaluated the effect of concurrent therapy with Ferriprox and deferoxamine in patients with thalassaemia major, who previously received the standard chelation monotherapy with subcutaneous deferoxamine and had mild to moderate cardiac iron loading (myocardial T2* from 8 to 20 ms). Following randomization, 32 patients received deferoxamine (34.9 mg/kg/day for 5 days/week) and Ferriprox (75 mg/kg/day) and 33 patients received deferoxamine monotherapy (43.4 mg/kg/day for 5 days/week). After one year of study therapy, patients on concurrent chelation therapy had experienced a significantly greater reduction in serum ferritin (1 574 µg/l to 598 µg/l with concurrent therapy vs. 1 379 µg/l to 1 146 µg/l with deferoxamine monotherapy, p<0.001), significantly greater reduction in myocardial iron overload, as assessed by an increase in MRI T2* (11.7 ms to 17.7 ms with concurrent therapy vs. 12.4 ms to 15.7 ms with deferoxamine monotherapy, p=0.02) and significantly greater reduction in liver iron concentration, also assessed by an increase in MRI T2* (4.9 ms to 10.7 ms with concurrent therapy vs. 4.2 ms to 5.0 ms with deferoxamine monotherapy, p<0.001).

Study LA37-1111 was conducted to evaluate the effect of single therapeutic (33 mg/kg) and supratherapeutic (50 mg/kg) oral doses of deferiprone on the cardiac QT interval duration in healthy subjects. The maximum difference between the LS means of the therapeutic dose and placebo was 3.01 ms (95% one-sided UCL: 5.01 ms), and between the LS means of the supratherapeutic dose and placebo was 5.23 ms (95% one-sided UCL: 7.19 ms). Ferriprox was concluded to produce no significant prolongation of the QT interval.

5.2 Pharmacokinetic properties

Absorption

Deferiprone is rapidly absorbed from the upper part of the gastrointestinal tract. Peak serum concentration occurs 45 to 60 minutes following a single dose in fasted patients. This may be extended to 2 hours in fed patients.

Following a dose of 25 mg/kg, lower peak serum concentrations have been detected in patients in the fed state (85 µmol/l) than in the fasting state (126 µmol/l), although there was no decrease in the amount of deferiprone absorbed when it was given with food.

Biotransformation

Deferiprone is metabolised predominantly to a glucuronide conjugate. This metabolite lacks iron-binding capability due to inactivation of the 3-hydroxy group of deferiprone. Peak serum concentrations of the glucuronide occur 2 to 3 hours after administration of deferiprone.

Elimination

In humans, deferiprone is eliminated mainly via the kidneys; 75% to 90% of the ingested dose is reported as being recovered in the urine in the first 24 hours, in the form of free deferiprone, the glucuronide metabolite and the iron-deferiprone complex. A variable amount of elimination via the faeces has been reported. The elimination half-life in most patients is 2 to 3 hours.

Renal impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired renal function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 4 groups based on estimated glomerular filtration rate (eGFR): healthy volunteers (eGFR $\geq$ 90 mL/min/1.73m^2), mild renal impairment (eGFR 60-89 mL/min/1.73m^2), moderate renal impairment (eGFR 30–59 mL/min/1.73m^2), and severe renal impairment (eGFR 15–29 mL/min/1.73m^2). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC.

Regardless of the degree of renal impairment, the majority of the dose of Ferriprox was excreted in the urine over the first 24 hours as deferiprone 3-*O*-glucuronide. No significant effect of renal impairment was seen on systemic exposure to deferiprone. Systemic exposure to the inactive 3-*O*-glucuronide increased with decreasing eGFR. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with impaired renal function. The safety and pharmacokinetics of Ferriprox in patients with end stage renal disease is unknown.

Hepatic impairment

An open-label, non-randomized, parallel group clinical study was conducted to evaluate the effect of impaired hepatic function on the safety, tolerability, and pharmacokinetics of a single 33 mg/kg oral dose of Ferriprox film-coated tablets. Subjects were categorized into 3 groups based on the Child-Pugh classification score: healthy volunteers, mild hepatic impairment (Class A: 5– 6 points), and moderate hepatic impairment (Class B: 7– 9 points). Systemic exposure to deferiprone and to its metabolite deferiprone 3-*O*-glucuronide was assessed by the PK parameters C_{max} and AUC. Deferiprone AUCs did not differ between treatment groups, but C_{max} was decreased by 20% in mildly or moderately hepatically impaired subjects compared with healthy volunteers. Deferiprone-3-*O*-glucuronide AUC was decreased by 10% and C_{max} by 20% in mildly and moderately impaired subjects compared with healthy volunteers. A serious adverse event of acute liver and renal injury was seen in one subject with moderate hepatic impairment. Based on the results of this study, no adjustment of the Ferriprox dose regimen is required in patients with mildly or moderately impaired hepatic function.

The influence of severe hepatic impairment on the pharmacokinetics of deferiprone and deferiprone 3-*O*-glucuronide has not been evaluated. The safety and pharmacokinetics of Ferriprox in patients with severe hepatic impairment is unknown.

5.3 Preclinical safety data

Non-clinical studies have been conducted in animal species including mice, rats, rabbits, dogs and monkeys.

The most common findings in non-iron-loaded animals at doses of 100 mg/kg/day and above were hematologic effects such as bone marrow hypocellularity, and decreased white blood cell (WBC), red blood cell (RBC) and/or platelet counts in peripheral blood.

Atrophy of the thymus, lymphoid tissues, and testis, and hypertrophy of the adrenals, were reported at doses of 100 mg/kg/day or greater in non-iron-loaded animals.

No carcinogenicity studies in animals have been conducted with deferiprone. The genotoxic potential of deferiprone was evaluated in a set of *in vitro* and *in vivo* tests. Deferiprone did not show direct mutagenic properties; however, it did display clastogenic characteristics in *in vitro* assays and in animals.

Deferiprone was teratogenic and embryotoxic in reproductive studies in non-iron-loaded pregnant rats and rabbits at doses at least as low as 25 mg/kg/day. No effects on fertility or early embryonic development were noted in non-iron-loaded male and female rats that received deferiprone orally at doses of up to 75 mg/kg twice daily for 28 days (males) or 2 weeks (females) prior to mating and until termination (males) or through early gestation (females). In females, an effect on the oestrous cycle delayed time to confirmed mating at all doses tested.

No prenatal and postnatal reproductive studies have been conducted in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Hydroxyethylcellulose
Glycerol (E422)
Concentrated hydrochloric acid (for pH adjustment)
Artificial cherry flavour
Peppermint oil
Sunset yellow (E110)
Sucralose (E955)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

After first opening, use within 35 days.

6.4 Special precautions for storage

Do not store above 30 ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

Amber polyethylene terephthalate (PET) bottles with child resistant closure (polypropylene), and a graduated measuring cup (polypropylene).

Each pack contains one bottle of 250 ml or 500 ml oral solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

8. MARKETING AUTHORISATION NUMBER

EU/1/99/108/002
EU/1/99/108/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 August 1999
Date of latest renewal: 21 September 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Eurofins PROXY Laboratories B.V.
Archimedesweg 25
2333 CM Leiden
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as a result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH should provide a patient card in each pack, the text of which is included in Annex IIIA. The patient card shall contain the following key messages:

- To increase patient awareness of the importance of regular monitoring of the neutrophil count during treatment with deferiprone
- To increase patient awareness of the significance of any symptoms of infection while taking deferiprone
- To warn women of childbearing age to not become pregnant because deferiprone may seriously harm the unborn baby.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

500 MG FILM-COATED TABLETS

BOTTLE OF 100 TABLETS

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

PATIENT CARD inside

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ferriprox 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

500 MG FILM-COATED TABLETS

BOTTLE OF 100 TABLETS

LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 500 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 500 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi (logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLES OF 250 ML AND 500 ML ORAL SOLUTION

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 100 mg deferiprone (25 g deferiprone in 250 ml).
Each ml of oral solution contains 100 mg deferiprone (50 g deferiprone in 500 ml).

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

250 ml
500 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

PATIENT CARD inside

8. EXPIRY DATE

EXP

After first opening, use within 35 days.

Date opened: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/002
EU/1/99/108/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ferriprox 100 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLES OF 250 ML AND 500 ML ORAL SOLUTION

LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 100 mg/ml oral solution
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of oral solution contains 100 mg deferiprone (25 g deferiprone in 250 ml).
Each ml of oral solution contains 100 mg deferiprone (50 g deferiprone in 500 ml).

3. LIST OF EXCIPIENTS

Contains sunset yellow (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

250 ml
500 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 35 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi (logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/002
EU/1/99/108/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1 000 MG FILM-COATED TABLETS

BOTTLE OF 50 TABLETS

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 1 000 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 000 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

50 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

PATIENT CARD inside

8. EXPIRY DATE

EXP

After first opening, use within 50 days.

Date opened: _____

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ferriprox 1000 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

1 000 MG FILM-COATED TABLETS

BOTTLE OF 50 TABLETS

LABEL

1. NAME OF THE MEDICINAL PRODUCT

Ferriprox 1 000 mg film-coated tablets
deferiprone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 000 mg deferiprone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

50 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After first opening, use within 50 days.

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.
Keep the bottle tightly closed in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Chiesi (logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/108/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PATIENT CARD

((Back Cover))

PREGNANCY, FERTILITY, LACTATION

Do not take Ferriprox if you are pregnant, trying to become pregnant, or are breastfeeding Ferriprox may seriously harm the baby. If you are pregnant, or breast-feeding during treatment with Ferriprox, tell your doctor and get medical advice immediately.

Women of childbearing potential are recommended to use effective contraception during the treatment with Ferriprox, and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. Ask your doctor which method is best for you.

4

((Front Cover))

PATIENT CARD

Important Safety Reminders for Patients taking Ferriprox (deferiprone)

Prescribing doctor: _____

Tel: _____

1

((Inside 1))

MONITORING YOUR WHITE BLOOD CELL COUNT WITH FERRIPROX

There is a small chance that you may develop agranulocytosis (very low white blood cell count) while taking Ferriprox, which may lead to a serious infection. Even though agranulocytosis only affects 1 to 2 out of 100 users, it is important to monitor your blood on a regular basis.

2

((Inside 2))

Make sure you do the following:

1. Have your blood monitored on a weekly basis for the first one year of treatment with Ferriprox and as regularly as your doctor recommends thereafter.

2. If you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.

3

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ferriprox 500 mg film-coated tablets
deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- A patient card is attached to the carton. You should detach, complete, read the patient card carefully and carry it with you. Provide this patient card to your doctor if you develop infection symptoms such as a fever, sore throat or flu-like symptoms.

What is in this leaflet

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is an iron chelator, a type of medicine that removes excess iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox
- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions
- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient card attached to the carton. If

you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.
- if you are human immunodeficiency virus (HIV) positive or if your liver or kidney function is severely impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox
Do not take medicines known to cause neutropenia or agranulocytosis (see "Do not take Ferriprox"). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids at the same time as taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding
Ferriprox may cause harm to unborn babies when used by pregnant women. Ferriprox must not be used during pregnancy unless clearly necessary. If you are pregnant or you become pregnant during treatment with Ferriprox, get medical advice immediately.

Both female and male patients are recommended to take special precautions in their sexual activity if there is any possibility for pregnancy to occur: Women of childbearing potential are recommended to use effective contraception during treatment with Ferriprox and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. This should be discussed with your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient card attached to the carton.

Driving and using machines
Not relevant.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food; however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should
There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox
Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):
- abdominal pain;
- nausea;
- vomiting;
- reddish/brown discolouration of urine.

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):
- low white blood cell count (agranulocytosis and neutropenia);
- headache;
- diarrhoea;
- increase in liver enzymes;
- fatigue;
- increase in appetite.

Not known (frequency cannot be estimated from the available data):
- allergic reactions including skin rash or hives.

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Do not store above 30 ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains
The active substance is deferiprone. Each 500 mg tablet contains 500 mg deferiprone.

The other ingredients are:
tablet core: microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica
coating: hypromellose, macrogol, titanium dioxide

What Ferriprox looks like and contents of the pack
White to off-white, capsule-shaped, film-coated tablet imprinted “APO” bisect “500” on one side, plain on the other. The tablet is 7.1 mm x 17.5 mm x 6.8 mm and scored. The tablet can be divided into equal halves. Ferriprox is packaged in bottles of 100 tablets.

Marketing Authorisation Holder:
Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma
Italy

Manufacturer:
Eurofins PROXY Laboratories B.V.
Archimedesweg 25
2333 CM Leiden
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Chiesi sa/nv
Tél/Tel: + 32 (0)2 788 42 00

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ExCEEd Orphan Distribution d.o.o.
Тел.: +359 87 663 1858

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Sverige
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Tel: +46 8 753 35 20

This leaflet was last revised in .

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Ferriprox 100 mg/ml oral solution
deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- A patient card is attached to the carton. You should detach, complete, read the patient card carefully and carry it with you. Provide this patient card to your doctor if you develop infection symptoms such as a fever, sore throat or flu-like symptoms.

What is in this leaflet

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is an iron chelator, a type of medicine that removes excess iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox
- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions
- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient card attached to the carton. If

you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.
– if you are human immunodeficiency virus (HIV) positive or if your liver or kidney function is severely impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox
Do not take medicines known to cause neutropenia or agranulocytosis (see "Do not take Ferriprox"). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids at the same time as taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding
Ferriprox may cause harm to unborn babies when used by pregnant women. Ferriprox must not be used during pregnancy unless clearly necessary. If you are pregnant or you become pregnant during treatment with Ferriprox, get medical advice immediately.

Both female and male patients are recommended to take special precautions in their sexual activity if there is any possibility for pregnancy to occur: Women of childbearing potential are recommended to use effective contraception during treatment with Ferriprox and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. This should be discussed with your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient card attached to the carton.

Driving and using machines
Not relevant.

Ferriprox oral solution contains sunset yellow (E110)
Sunset yellow (E110) is a colouring agent which may cause allergic reactions.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Use the measuring cup to measure the volume prescribed by your doctor. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should
There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox
Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):
- abdominal pain;
- nausea;
- vomiting;
- reddish/brown discolouration of urine.

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):
- low white blood cell count (agranulocytosis and neutropenia);
- headache;
- diarrhoea;
- increase in liver enzymes;
- fatigue;
- increase in appetite.

Not known (frequency cannot be estimated from the available data):
- allergic reactions including skin rash or hives.

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

After first opening, use within 35 days. Do not store above 30 ºC. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains
The active substance is deferiprone. Each ml of oral solution contains 100 mg deferiprone.

The other ingredients are: purified water; hydroxyethylcellulose; glycerol (E422); concentrated hydrochloric acid (for pH adjustment); artificial cherry flavour; peppermint oil; sunset yellow (E110); sucralose (E955). See section 2. 'Ferriprox oral solution contains sunset yellow (E110)'.

What Ferriprox looks like and contents of the pack
Clear, reddish orange coloured liquid. Ferriprox is packaged in bottles of 250 ml or 500 ml.

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Via Palermo 26/A
43122 Parma
Italy

Manufacturer:
Eurofins PROXY Laboratories B.V.
Archimedesweg 25
2333 CM Leiden
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in .

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

Ferriprox 1 000 mg film-coated tablets
deferiprone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.
- A patient card is attached to the carton. You should detach, complete, read the patient card carefully and carry it with you. Provide this patient card to your doctor if you develop infection symptoms such as a fever, sore throat or flu-like symptoms.

What is in this leaflet

1. What Ferriprox is and what it is used for

Ferriprox contains the active substance deferiprone. Ferriprox is an iron chelator, a type of medicine that removes excess iron from the body.

Ferriprox is used to treat iron overload caused by frequent blood transfusions in patients with thalassaemia major when current chelation therapy is contraindicated or inadequate.

2. What you need to know before you take Ferriprox

Do not take Ferriprox
- if you are allergic to deferiprone or any of the other ingredients of this medicine (listed in section 6).
- if you have a history of repeated episodes of neutropenia (low white blood cell (neutrophil) count).
- if you have a history of agranulocytosis (very low white blood cell (neutrophil) count).
- if you are currently taking medicines known to cause neutropenia or agranulocytosis (see “Other medicines and Ferriprox”).
- if you are pregnant or breast-feeding.

Warnings and precautions
- the most serious side effect that may occur while taking Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. Because white blood cells help to fight infection, a low neutrophil count may place you at risk of developing a serious and potentially life-threatening infection. To monitor for neutropenia, your doctor will ask you to have a blood test (to check your white blood cell count) performed regularly, as frequently as every week, while you are being treated with Ferriprox. It is very important for you to keep all of these appointments. Please refer to the patient card attached to the carton. If

you get any symptoms of infection such as fever, sore throat or flu-like symptoms, immediately seek medical attention. Your white blood cell count must be checked within 24 hours in order to detect potential agranulocytosis.
– if you are human immunodeficiency virus (HIV) positive or if your liver or kidney function is severely impaired, your doctor may recommend additional tests.

Your doctor will also ask you to come in for tests to monitor body iron load. In addition he or she might ask you to undergo liver biopsies.

Other medicines and Ferriprox
Do not take medicines known to cause neutropenia or agranulocytosis (see "Do not take Ferriprox"). Tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines, including medicines obtained without a prescription.

Do not take aluminium-based antacids at the same time as taking Ferriprox.

Please consult with your doctor or pharmacist before taking vitamin C with Ferriprox.

Pregnancy and breast-feeding
Ferriprox may cause harm to unborn babies when used by pregnant women. Ferriprox must not be used during pregnancy unless clearly necessary. If you are pregnant or you become pregnant during treatment with Ferriprox, get medical advice immediately.

Both female and male patients are recommended to take special precautions in their sexual activity if there is any possibility for pregnancy to occur: Women of childbearing potential are recommended to use effective contraception during treatment with Ferriprox and for 6 months after the last dose. Men are recommended to use effective contraception during treatment and for 3 months after the last dose. This should be discussed with your doctor.

Do not use Ferriprox if you are breast-feeding. Please refer to the patient card attached to the carton.

Driving and using machines
Not relevant.

3. How to take Ferriprox

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. The amount of Ferriprox that you take will depend on your weight. The usual dose is 25 mg/kg, 3 times per day, for a total daily dose of 75 mg/kg. The total daily dose should not exceed 100 mg/kg. Take your first dose in the morning. Take your second dose midday. Take your third dose in the evening. Ferriprox can be taken with or without food; however, you may find it easier to remember to take Ferriprox if you take it with your meals.

If you take more Ferriprox than you should
There are no reports of acute overdose with Ferriprox. If you have accidentally taken more than the prescribed dose, you should contact your doctor.

If you forget to take Ferriprox
Ferriprox will be most effective if you do not miss any doses. If you do miss one dose take it as soon as you remember and take your next dose at its regularly scheduled time. If you miss more than one dose do not take a double dose to make up for forgotten individual doses, just continue with your normal schedule. Do not change your daily dose without first talking to your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effect of Ferriprox is a very low white blood cell (neutrophil) count. This condition, known as severe neutropenia or agranulocytosis, has occurred in 1 to 2 out of 100 people who have taken Ferriprox in clinical studies. A low white blood cell count can be associated with a serious and potentially life-threatening infection. Report immediately to your doctor any symptoms of infection such as: fever, sore throat or flu-like symptoms.

Very common side effects (may affect more than 1 in 10 people):
- abdominal pain;
- nausea;
- vomiting;
- reddish/brown discolouration of urine.

If you experience nausea or vomiting, it may help to take your Ferriprox with some food. Discoloured urine is a very common effect and is not harmful.

Common side effects (may affect up to 1 in 10 people):
- low white blood cell count (agranulocytosis and neutropenia);
- headache;
- diarrhoea;
- increase in liver enzymes;
- fatigue;
- increase in appetite.

Not known (frequency cannot be estimated from the available data):
- allergic reactions including skin rash or hives.

Events of joint pain and swelling ranged from mild pain in one or more joints to severe disability. In most cases, the pain disappeared while patients continued taking Ferriprox.

Neurological disorders (such as tremors, walking disorders, double vision, involuntary muscle contractions, problems with movement coordination) have been reported in children who had been voluntarily prescribed more than double the maximum recommended dose of 100 mg/kg/day for several years and have also been observed in children with standard doses of deferiprone. The children recovered from these symptoms after Ferriprox discontinuation.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ferriprox

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after EXP. The expiry date refers to the last day of that month.

Do not store above 30 ºC. Keep the bottle tightly closed in order to protect from moisture. After first opening, use within 50 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ferriprox contains
The active substance is deferiprone. Each 1 000 mg tablet contains 1 000 mg deferiprone.

The other ingredients are:
tablet core: methylcellulose, crospovidone, magnesium stearate
coating: hypromellose, hydroxypropyl cellulose, macrogol, titanium dioxide

What Ferriprox looks like and contents of the pack
White to off-white, capsule-shaped, film-coated tablet imprinted “APO” bisect “1000” on one side, plain on the other. The tablet is 7.9 mm x 19.1 mm x 7 mm and scored. The tablet can be divided into equal halves. Ferriprox is packaged in bottles of 50 tablets.

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Manufacturer:
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